REMARKS/ARGUMENTS

In response to the Office Action of December 28, 2004, Applicants request re-examination and reconsideration of this application for patent pursuant to 35 U.S.C. 132.

Claim Status/Support for Amendments

Claims 1, 39 and 44-46 have been amended. Claims 2-38 were cancelled in a previous response (December 10, 2004). Claims 39-46 are withdrawn from consideration. It is understood that claims 39-46, drawn to the non-elected invention, will remain pending, albeit withdrawn from prosecution on the merits at this time. If the examined claim of the Group I invention is deemed to be allowable, rejoinder of the remaining claims (39-46) in accordance with the decision in *In re Ochiai* is respectfully requested; since the remaining claims (39-46) are limited to the use of the biopolymer marker of claim 1.

Claim 1 is under examination. Claims 1 and 39-46 remain pending in the instant application.

No new matter has been added by the amendments to the specification made herein.

The title of the invention has been amended to clearly indicate the invention to which the claims are drawn and to correct a punctuation error in the reciting of Alzheimer's disease

(Alzheimers corrected to recite Alzheimer's).

In the "Background of the Invention" section a punctuation error was corrected at page 1, line 23.

The description of the reference at page 5 has been amended to correct a typographical error in the international application number. The corresponding international publication number has also been added.

The "Description of the Figures" section has been amended to add sequence identification numbers, clearly indicate that Figures 2, 4 and 5 show the mass spectrum profiles of the disclosed biopolymer markers, and to correct a punctuation error in the reciting of Alzheimer's disease (Alzheimers corrected to recite Alzheimer's).

Several protocols at pages 40-45 have been amended to properly identify trademark names (SEPHAROSE, TRITON, TRIS and EPPENDORF). The protocol titles at page 41 (line 10), page 42 (lines 1 and 16) and page 43 (lines 7 and 20) were underlined in the original disclosure and do not indicate amended text.

The paragraph at page 46 was amended to correct a punctuation error in the reciting of Alzheimer's disease (Alzheimers corrected to recite Alzheimer's).

In the "Detailed Description" section, the term "cerebrospinal fluid" has been added to define the abbreviation "CSF" at page 49, line 16 in order to provide explicit support for cerebrospinal

fluid as recited in claim 41. "CSF" is a well known abbreviation for cerebrospinal fluid in the biochemical art. A typographical error within the same paragraph has also been amended (skill replaced skilled).

The abstract has been amended to remove the legal phraseology ("said").

No new matter has been added by the amendments to the claims made herein.

Claim 1 has been amended to explicitly claim the biopolymer marker (SEQ ID NO:3). The term "biopolymer marker" is used throughout the specification as originally filed, see, for example, page 1, line 8.

Claim 39 has been amended to clearly disclose the relationship between the presence of the claimed biopolymer marker (SEQ ID NO:3) and Alzheimer's disease. Claim 39 has also been amended to explicitly indicate how the presence of the claimed biopolymer marker is determined from mass spectrum profiles. The changes to claim 39 find basis throughout the specification as originally filed, see, for example, page 35, lines 14-18, page 46, lines 8-18 and Figure 3.

Claim 44 has been amended to correspond with the biopolymer marker of claim 1 (as amended herein). Support for various types of kits can be found in the original disclosure, see for example, page 36, lines 9-12 and page 47, line 14 to page 48, line 23.

Claims 45 and 46 have been amended to provide proper antecedent basis for the term "kit" in claim 44 (as amended herein).

Restriction

The Examiner has determined that the requirement for restriction is still proper and therefore has made the requirement final.

Applicants have claimed the biopolymer markers (SEQ ID NOS:1-3)in a Markush-type grouping indicating that SEQ ID NOS:1-3 are alternatively usable (MPEP 803.02). In contrast to Applicants' presentation of SEQ ID NOS:1-3 in a Markush-type grouping, the Sequence Election Requirement presents each of SEQ ID NOS:1-3 as unrelated patentably distinct sequences, thus introducing a contradiction into the prosecution history. Such contradictions can potentially diminish the value of any patent that may issue from the instant application. Since Applicants are required to elect a Group (and a single sequence) for prosecution on the merits, one reading the prosecution history may incorrectly assume that Applicants admit that the biopolymer markers of SEQ ID NOS:1-3 are separate and distinct inventions.

Request for Rejoining of Claims

Considering that claims 39-46 are limited to the use of SEQ

ID NO:3 a search of these claims would encompass this specific peptide. The instant application is related in claim format to several other applications, both pending and issued, of which serial number 09/846,352 is exemplary. In an effort to maintain equivalent scope in all of these applications, Applicants respectfully request that the Examiner consider rejoining claims 39-46 in the instant application, which are currently drawn to non-elected Groups, with claim 1 of the elected Group under the decision in *In re Ochiai* (MPEP 2116.01), upon the Examiner's determination that claim 1 of the elected invention is allowable and in light of the overlapping search. If the biopolymer marker peptide of SEQ ID NO:3 is found to be novel, methods and kits limited to its use should also be found novel.

Information Disclosure Statement

The Examiner has pointed out that the listing of references in the specification is not a proper Information Disclosure Statement. 37 CFR 1.98(b) requires a list of all patents, publications or other information submitted for consideration by the Office, and MPEP 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Thus, the Examiner indicates that unless the Examiner on PTO-892 form or Applicant on PTO-1449 form has cited the references they have not been considered.

The Examiner indicates that the Information Disclosure Statement filed on March 12, 2002 has been considered as to the merits prior to the first action.

The references cited within the specification but not included in the above-mentioned Information Disclosure Statement provide general information relating to background information and/or the state of the art, but were not deemed pertinent to the patentability of the claimed invention.

Oath/Declaration

A new oath or declaration has been required by the Examiner because while the original oath filed on March 5, 2002 contains the signature of Dr. John Marshall (inventor 2), the date of signature is omitted.

Applicants are currently in the process of preparing a new oath and will forward such oath to the Examiner as soon as it is completed and properly executed.

Objections to the Specification

The Examiner notes that the specification has not been checked to the extent necessary to determine the presence of all possible minor errors.

A new title has been required by the Examiner since the original title was deemed not descriptive. The Examiner alleges

that the title is drawn to markers which are indicative of age-matched control but the claimed marker set forth in SEQ ID NO:3 is for Alzheimer's disease. The Examiner further alleges that it is not clear as to what applicant intends to encompass by the wording "age-matched control". The Examiner suggests that the title be amended to read "Protein Biopolymer Markers Indicative Of Alzheimer's Disease".

The title has been amended according to the Examiner's suggestion. An "age-matched control" is a sample selected from a patient who is the same or approximately the same age as an Alzheimer's patient from whom a sample is selected. "Age-matching" of controls is common practice in Alzheimer's disease research.

The Examiner notes the use of trademarks in the application (i.e. SEPHAROSE at page 41, lines 4 and 5 and TRITON at page 42, line 12) which should be capitalized wherever they appear and be accompanied by the generic terminology. The Examiner further notes that although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks.

Applicants have amended the specification at pages 40-45 to properly identify trademark names (SEPHAROSE, TRITON, TRIS and EPPENDORF).

The Examiner points out guidelines for the proper language and

format of an abstract of a patent application and objects to the abstract of the instant application as it recites the legal phraseology "said".

The abstract of the instant application has been amended herein to remove the legal phraseology "said".

Applicants have now addressed all of the Examiner's objections and respectfully request that the objections to the specification be withdrawn.

Sequence Compliance

The Examiner asserts that the application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2). The Examiner notes that the application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. The Examiner asserts that Figure 5 recites sequences without including the appropriate sequence identification numbers.

The Examiner has requested that Applicant return a copy of the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures with the Response to the Office Action mailed on

December 28, 2004; however, Applicants note that no such Notice (form PTO-1661) was attached to the Office Action. Applicants respectfully request that this notice be included within the Examiner's next communication to the Applicants.

Several sequences shown in Figure 5 were inadvertently omitted from the original Sequence Listing filed on March 5, 2002. Thus, Applicants herein provide a Substitute Sequence Listing in both paper and computer-readable form in order to identify the six sequences disclosed in the instant specification with sequence identification numbers. The computer-readable form of the Substitute Sequence Listing is identical to the paper form of the Substitute Sequence Listing. The sequences listed in the Substitute Sequence Listing have been identified as SEQ ID NOS: 1-6 and are disclosed at page 46 and/or in Figure 5 of the originally filed specification, thus the Substitute Sequence Listing, in both paper and computer-readable form, contains no new matter.

The instant specification has been amended at page 37 to include sequence identification numbers for the amino acid sequences disclosed in the figures.

Applicants respectfully submit that the instant application is now in compliance with the sequence requirements of 37 CFR 1.821-1.825. However, should the Substitute Sequence List (paper and disk copies) not be found fully in compliance with all requirements, Applicants respectfully request prompt notice by

telephone in order to accomplish expedited correction within the allotted time period.

Rejection under 35 USC 101

Claim 1, as presented on December 10, 2004, stands rejected under 35 USC 101 because the claimed invention allegedly is not supported by a either a specific, substantial, credible or asserted utility or a well-established utility.

Applicants respectfully disagree with the Examiner's contention and assert that the claimed invention has both a specific and a well-established utility.

The Examiner asserts that applicants have disclosed in the specification that SEQ ID NO:3 is measurable in patients with Alzheimer's disease but is undetectable or regulated differently in normal patients.

Applicants respectfully assert that this statement made by the Examiner is incorrect.

Page 46 of the instant specification indicates that practice of the disclosed procedures identifies the peptide of SEQ ID NO:3 as related to Alzheimer's disease. Contrary to the Examiner's assertion, no assumptions regarding the presence and/or regulation of the peptide (SEQ ID NO:3) are found at page 46 of the instant specification.

Additionally, the Examiner asserts that the disclosure appears

to require not only SEQ ID NO:3 but a combination of SEQ ID NOS:1-3 for the identification of Alzheimer's disease.

Applicants respectfully assert that this statement made by the Examiner is also incorrect.

No where does the specification indicate that a combination of markers (SEQ ID NOS:1-3) is an absolute requirement for the identification of Alzheimer's disease through use of the disclosed methods.

At page 10 of the Office Action mailed on December 28, 2004, the Examiner asserts that SEQ ID NO:3 does not appear to be a marker for Alzheimer's disease.

Applicants respectfully disagree with the Examiner's line of reasoning and assert that SEQ ID NO:3 is useful for diagnosis and/or treatment of Alzheimer's disease since it was found to evidence a link to Alzheimer's disease (an "asserted" utility).

The Examiner is reminded that an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement under 35 USC 101 (see MPEP 2107.02 III A). Thus, the requirements of 35 USC 101 are met solely by Applicants above assertion regarding the use of the claimed peptide (SEQ ID NO:3).

Furthermore, Applicants' statement of an asserted utility also constitutes a specific and substantial utility that is supported by the specification as originally filed (see page 1, lines 5-13;

page 35, lines 14-18; page 46, lines 8-18; and Figures 1 and 3).

The claimed peptide (SEQ ID NO:3) does not evidence a link to a myriad of unspecified diseases but rather evidences a link to a specific disease, Alzheimer's disease, thus the invention has a specific utility.

Furthermore, advances in diagnosis and treatment of Alzheimer's disease are highly desirable considering that the elderly population is increasing. The claimed peptide (SEQ ID NO:3) represents an advance in Alzheimer's research; a "real-world" use. Thus, the claimed peptide (SEQ ID NO:3) additionally has a substantial utility.

It has been established that where an applicant has specifically asserted that an invention has a particular utility, the assertion cannot be simply dismissed by Office personnel as being "wrong", even when there may be a reason to believe that the assertion is not entirely accurate (see MPEP 2107.02 III B).

Although the Examiner should regard Applicants' statement of asserted utility sufficient to satisfy the requirements of 35 USC 101, the Examiner lists several additional reasons which allegedly support her argument that the claimed invention has no utility.

The Examiner asserts that no clear difference in up and down regulation of the marker can be determined; the correlation with respect to Alzheimer's disease is not evident and thus SEQ ID NO:3 does not appear to be a marker for Alzheimer's disease.

Applicants respectfully disagree with the Examiner's assertions.

Figure 1 is a photograph of a gel showing the results of DEAE (anion exchanging) resin column chromatography as carried out with a set of 9 samples; 4 serum samples from Alzheimer's disease patients (lanes 1-4, as read from the left), 4 serum samples from patients age matched with the Alzheimer's disease patients (lanes 5-8, as read from the left) and 1 sample of normal serum (pooled from a plurality of patients (lane 9, as read from the left). Lane 10 contained the molecular weight markers. Multiple proteins were examined, thus band numbers point to areas of the gel from which particular protein fragments were elucidated.

Figure 3 is a photograph of a gel similar to that of Figure 1; with the exception of the numbered bands. Three bands are labeled in the gel shown in Figure 3; C1 (age matched), C3 (age matched) and C2 (Alzheimer's disease). It can be observed that bands C1 and C2, from which the claimed marker (SEQ ID NO:3) was obtained and analyzed, are not of the same intensity, and further that band C1 is of greater intensity than corresponding band C2. Expression of the claimed marker (SEQ ID NO:3) is decreased or absent in Alzheimer's disease according to the data shown in the gel of Figure 3. Thus, contrary to the Examiner's assertion, a clear difference in up and down regulation of the marker can be determined from the data presented in the instant specification.

In the medical arts proteins found to be differentially expressed between "disease" and "normal" are frequently identified as potential targets for diagnostics and/or therapeutics. For example, when a peptide is identified in a body fluid sample from an Alzheimer's patient, it is immediately recognized as a potential diagnostic marker, even if the involvement of the peptide in the pathology of Alzheimer's disease is unknown. One of skill in the art would be familiar with this practice since it has been known in the art since at least 1992. See attached abstract of Gunnersen et al. (Proceedings of the National Academy of Science USA 89(24):11949-11953 1992; reference 1) in which the detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer's disease patients lead to the suggestion of glutamine synthetase as a potential diagnostic biochemical marker. Thus, when one of skill in the art observes the claimed peptide differentially expressed between Alzheimer's disease patients and age matched control patients; one of skill in the art would connect the peptide with potential diagnostics and/or therapeutics for Alzheimer's disease and would immediately appreciate why applicants regard the claimed peptide (SEQ ID NO:3) as useful, indicating that the utility of the claimed peptide (SEQ ID NO:3) is well-established. Thus, contrary to the Examiner's assertion a correlation between the claimed peptide (SEQ ID NO:3) and Alzheimer's disease is evident.

The claimed peptide is identified as a fragment of

apolipoprotein J precursor protein at page 46, lines 8-18. Apolipoprotein J protein is also known as clusterin; see attached abstract of Moulson et al. (Journal of Cell Physiology 180(3):355-364 1999; reference 2). Clusterin (ApoJ) is a glycoprotein known to be expressed in response to tissue injury and has been associated with the pathology of Alzheimer's disease; see attached abstracts of Giannakopoulos et al. (Acta Neuropathology (Berl) 95(4):387-394 1998; reference 3) and BV Zlokovic (Life Science 59(18):1483-1497 1996; reference 4). It has been suggested that ApoJ exhibits an anti-amyloidogenic effect as it acts as a carrier protein of amyloid beta in body fluids, thus keeping it (amyloid beta) in soluble form (BV Zlokovic Life Science 59(18):1483-1497 1996; reference 4). Soluble amyloid beta is not deposited to form the amyloid plaques which are characteristic of Alzheimer's disease. It has also been suggested that low cellular expression of clusterin may be associated with the neuronal degeneration and death seen in Alzheimer's disease (Giannakopoulos et al. Acta Neuropathology (Berl) 95(4):387-394 1998; reference 3). A skilled artisan would find the data disclosed by the instant inventors to be reasonable since lack of ApoJ (claimed biopolymer marker) is associated with the pathology of Alzheimer's disease and expression of the claimed biopolymer marker was found to be decreased or absent in samples obtained from Alzheimer's disease patients.

Therefore, one of ordinary skill in the art would recognize the linkage between SEQ ID NO:3 and Alzheimer's disease and thus would also find the suggestion of SEQ ID NO:3 as a marker for Alzheimer's disease entirely reasonable.

Accordingly, Applicants assert that the claimed invention has both a specific and a well-established utility and respectfully request that this rejection under 35 USC 101 now be withdrawn.

Rejection under 35 USC 112, second paragraph

Claim 1, as presented on December 10, 2004, stands rejected under 35 USC 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The Examiner asserts that claim 1 is vague and indefinite because the biopolymer is "diagnostic" for Alzheimer's disease. "Diagnostic" reads on not only the detection of the disease but also the analysis of the cause or nature of the disease. It is not clear how the biopolymer marker will analyze the cause or nature of Alzheimer's disease. Applicants' intended meaning of "diagnostic" is not defined by the claims or the specification. The specification does not provide a standard for ascertaining the requisite degree and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The Examiner suggests that the claim merely recite "detection of" Alzheimer's

disease in order to obviate this rejection.

Applicants respectfully disagree with the Examiner's assertions.

The term "diagnostic" refers to the identification of a property or characteristic, usually regarding health of an individual, such as, identifying a disease linked with the property or characteristic. It is clear from the multiple disclosures in the instant specification that the term "diagnostic" or "diagnose" refers to the identification of a disease; see, for example, page 5, lines 12-20; page 31, lines 19-22; page 32, lines 7-10; page 36, lines 9-12; page 48, lines 9-11; page 52, lines 10-13 and page 53, lines 1-12. According to a search on the web site dictionary. com; the term "diagnostic" relates to or refers to use in diagnosis; serving to identify a particular disease or to a symptom or a distinguishing feature serving as supporting evidence in a diagnosis (see attached definition as accessed from the internet, reference 5).

Neither the art nor the specification suggests that "diagnostic" refers to anything other than identification of a disease. Thus, Applicants respectfully submit that the Examiner has no basis for asserting that the term "diagnostic" reads on not only the detection of the disease but also the analysis of the cause or nature of the disease.

However, in the interest of compact, efficient prosecution,

Applicants have amended the claim to remove the term "diagnostic".

Accordingly, Applicants have now clarified the metes and bounds of the claims and respectfully request that the above-discussed rejection under 35 USC 112, second paragraph be withdrawn.

Rejection under 35 USC 112, first paragraph

Claim 1, as presented on December 10, 2004, stands rejected under 35 USC 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner asserts that the claim contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Examiner makes the following assertions:

Claim 1 is directed to a biopolymer consisting of SEQ ID NO:3 indicative of Alzheimer's disease. The Examiner contends that the specification does not support this assertion. The specification (in particular page 46) and the figures do not definitively correlate the claimed marker consisting of SEQ ID NO:3 to Alzheimer's disease. The specification recites that the biopolymer consisting of SEQ ID NO:3 was found or regulated differently in the serum of patients suffering from Alzheimer's disease on page 46, but the specification does not contain any data supporting this

contention and the figures do not identify SEQ ID NO:3 as a definitive marker for Alzheimer's disease. Therefore, it is unclear how SEQ ID NO:3 was identified as "notable" or how it was deemed "evidentiary" of a disease state. There is nothing in the disclosure that would enable one to choose SEQ ID NO:3 as a notable sequence among an infinite number of possible proteins or peptides present in a patient sample.

Applicants respectfully disagree with all of the Examiner's assertions.

Although Applicants believe that the instant specification, as originally filed, fully supports the claim that an isolated peptide consisting of SEQ ID NO:3 is diagnostic for Alzheimer's disease, in the interest of compact, efficient prosecution, Applicants have removed the term "diagnostic" from the claims and note that the isolated peptide consisting of SEQ ID NO:3 is linked to Alzheimer's disease.

According to the web site dictionary.com the term "linked" refers to the condition of being associated with or connected to (see attached document as accessed from the internet; reference 6). The instant specification fully supports a connection and/or an association of the claimed peptide with Alzheimer's disease. The instant specification states at page 35, lines 14-18 that an objective of the invention is to evaluate samples containing a plurality of biopolymers for the presence of disease specific

biopolymer marker sequences which evidence a link to at least one specific disease state.

The "test of enablement" is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the prior art without undue experimentation (see MPEP 2164.01).

Furthermore, the decision in *In re Brandstadter* (179 USPQ 286; MPEP 2164.05) has established that the evidence provided by applicant (to overcome an enablement rejection) need not be conclusive but merely convincing to one of skill in the art.

Applicants respectfully submit that the instant specification provides sufficient evidence to convince one of skill in the art that the claimed peptide (SEQ ID NO:3) is linked and/or associated with Alzheimer's disease.

Claim 1 has been amended to specifically recite an isolated marker consisting of SEQ ID NO:3, a peptide which the instant specification identifies as related to Alzheimer's disease. Claim 1, as amended herein, does not recite that the claimed isolated peptide is diagnostic for Alzheimer's disease, nor does it recite that the claimed isolated peptide is related to Alzheimer's disease, even though Applicants believe that the specification, as originally filed, fully supports both of these recitations. Furthermore, the phrase "consisting of" is closed language and excludes any element, step or ingredient not specified in the

claims (see MPEP 2111.03). Thus, the scope of claim 1 is limited to this specific peptide (SEQ ID NO:3).

Figure 3 demonstrates that the biopolymer marker peptide (SEQ ID NO:3) is present in both body fluid samples obtained from Alzheimer's patients (band C2) and age matched control patients (bands C1 and C3); however decreased expression is seen in the samples obtained from Alzheimer's disease patients as compared with the samples obtained from the age matched control patients. Thus, a difference is seen between two comparable samples, suggesting that the differentially expressed marker peptide is linked to Alzheimer's disease.

The specification, as originally filed, provides a precise protocol on how to analyze the date obtained from the disclosed method. Page 25, line 16 to page 26, line 2 of the instant specification discloses a general outline of how to analyze the data obtained by carrying out the disclosed methods. Page 26, lines 6-13 of the instant specification further describes how samples were compared to develop data and indicates how biopolymer marker peptides were selected as notable sequences. This passage of the instant specification also discloses how certain peptides were selected from a plurality of molecules found within a sample and how peptides were deemed evidentiary of a disease state. Page 5, lines 12-20 also describes how biopolymer markers are evaluated according to the methods of the instant invention. Page 47, lines

3-5 of the instant specification clearly states the steps of the invention include obtaining a sample from a patient and conducting an MS analysis (mass spectrometry) on the sample. Mass spectrometry is commonly practiced and one of skill in the art would know how to analyze and obtain information from mass spectrometry profiles. It is clear that the data presented in the instant specification was obtained by carrying out mass spectrometry. Thus, Applicants assert that the specification, as originally filed, provides a precise protocol on how to analyze the data obtained by the disclosed protocol.

Additionally, Applicants respectfully submit that such protocols are common practice in the field of proteomics. For example, Lubec et al. (see attached abstract Journal Neural Transmission Supplement 57:161-177 1999; reference 7) disclose an experiment in which proteomic techniques, specifically electrophoresis and mass spectrometry, were carried out to detect differences in protein expression between Down's syndrome patients, Alzheimer's patients and "normal" control patients. In a manner similar to that of the instant inventors, Lubec et al. analyzed the increase and/or decrease in expression of a particular protein (DRP-2) when hypothesizing about the neuropathological findings in Alzheimer's disease and Down's syndrome.

Furthermore, Applicants assert that those of skill in the art are both highly knowledgeable and skilled and it is obvious that

no undue experimentation would be required for a skilled artisan to follow any of the electrophoretic, chromatographic and mass spectrometric protocols presented in the instant specification in order to use the claimed invention. One of skill in the art would be able to view a gel, such as that shown in Figure 3 from which the claimed peptide was identified (SEQ ID NO:3), and recognize a difference between two comparable samples (disease state vs. non-disease state) and further recognize that the peptides present within the gel are differentially expressed between the two sample types.

Figure 3 is a photograph of a gel showing the results of DEAE (anion-exchanging) column chromatography as carried out with a set of 9 samples; 4 serum samples from Alzheimer's disease patients (lanes 1-4, as read from the left), 4 serum samples from patients age matched with the Alzheimer's patients (lanes 5-8, as read from the left) and 1 sample of normal serum(pooled from different "normal" patients; lane 9, as read from the left).

The claimed biopolymer marker (SEQ ID NO:3) was found to be differentially expressed between Alzheimer's disease and age-matched normal through use of proteomics techniques. The field of proteomics was established in the mid-1990's, is well-studied and is expanding rapidly to advance medical diagnostics and therapeutics. In proteomics research, differential protein expression patterns between normal and diseased cells are routinely

analyzed and compared (see attached press release from Scimagix, Inc. as accessed from the internet; reference 8). Expression proteomics is the large-scale analysis of protein expression and function in which the goal is to detect and identify all-or a subset-of the proteins present in a particular sample and find out which of these proteins are present, absent or differentially expressed in a related sample subject to a specific variation (see attached document GIGA Proteomics Facility, Belgium as accessed from the internet; reference 9). Proteomics techniques make it possible for researchers to immediately highlight proteins that are differentially abundant in one state versus another (for example, tumor vs. normal or before and after treatment; see attached article Liotta et al. Breast Cancer Research 2:13-14 1999 as accessed from the internet, page 2, second paragraph; reference 10). A protein found only in a diseased sample may prove to be a useful drug target or diagnostic marker (see attached document GIGA Proteomics Facility, Belgium as accessed from the internet; reference 9). Thus, considering that markers discovered through the use of well-known proteomics techniques are often associated with potential diagnostics and/or therapeutics, when one of skill in the art observes the claimed biopolymer marker differentially expressed between Alzheimer's disease and age-matched normal; one of skill in the art would know how to identify such biopolymer marker and would connect such biopolymer marker with potential diagnostics

and/or therapeutics for Alzheimer's disease.

The data presented in the figures, derived from the working examples, discloses that the claimed peptide (SEQ ID NO:3) is differentially expressed between Alzheimer's disease and a "normal" physiological state of patients age matched to the Alzheimer's patients, thus it can be reasonably predicted that such peptide is linked to Alzheimer's disease. Furthermore, the figures identify SEQ ID NO:3 and the specification discloses how such a sequence was identified as a notable sequence in relation to Alzheimer's disease.

Thus, Applicants contend a skilled practitioner would find that the data presented in the instant specification is convincing with regard to a link between the claimed biopolymer marker peptide (SEQ ID NO:3) and Alzheimer's disease.

Considering the above comments, it is clear that both the specification and the prior art disclose how to make and use the instant invention. Accordingly, Applicants respectfully contend that the instant invention satisfies the "test for enablement" since one skilled in the art could make or use the invention from the disclosures in the specification coupled with information known in the prior art without undue experimentation.

The Examiner makes a series of assertions regarding the enablement of subject matter which is not claimed, including the following:

The Examiner asserts that there is no correlation between the procedure for screening samples from patients suspected of having a variety of different diseases, the presence/absence of SEQ ID NO:3; and the determination, prediction, assessment of at least one particular disease state like Alzheimer's disease. There is no disclosure enabling the use of the biopolymer marker with regard to regulating the presence or absence of said marker. The disclosure is lacking any teaching for how the identified sequence will be utilized to identify therapeutic avenues and regulation of a disease state. There is no disclosure designating how the sequence could be utilized therein, enabling one of ordinary skill in the art to use the sequence in the diagnostic method.

The Examiner is reminded that all questions of enablement should be evaluated against the claimed subject matter and the focus of the examination inquiry should be a question of whether everything within the scope of the claims is enabled (see MPEP 2164.08).

Accordingly, an Applicant is not required to enable material which is not claimed. The pending claims do not recite any disease state other than Alzheimer's disease, nor do the pending claims recite identification of therapeutic avenues or methods of regulating the sequence or a disease state. Thus, no teachings regarding these issues are necessary in order to provide evidence for enablement of the pending claims.

The Examiner asserts that Applicants have not set forth any supporting evidence that suggests that any of the sequences (in particular SEQ ID NO:3) are unique molecular markers for Alzheimer's disease or any other disease and the prior art teaches that disease markers are highly unpredictable and require extensive experimentation.

The guidelines for a "test of enablement" indicate that if a statement of utility in the specification contains within it a connotation of how to use, and/or the art recognizes that standard modes of administration are known and contemplated, 35 USC 112, is satisfied (see MPEP 2164.01(c)).

Additionally, it has been established that the mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it (see MPEP 2164.02).

Applicants assert that SEQ ID NO:3 is linked to Alzheimer's disease, however, do not claim that SEQ ID NO:3 is a unique marker for any particular disease or condition.

Although the prior art does not specifically recognize that the claimed SEQ ID NO:3 is related to Alzheimer's disease, it does recognize that when a peptide is identified in a body fluid sample from an Alzheimer's patient or appears to be differentially expressed between an Alzheimer's disease patient and a "normal" patient, it is immediately recognized as a potential diagnostic

marker, even if the involvement of the peptide in the pathology of Alzheimer's disease is unknown. One of skill in the art would be familiar with this practice since it has been known in the art since at least 1992. See attached abstract of Gunnersen et al. (Proceedings of the National Academy of Science USA 89(24):11949-11953 1992; reference 1) in which the detection of glutamine synthetase in the cerebrospinal fluid of Alzheimer's disease patients lead to the suggestion of glutamine synthetase as a potential diagnostic biochemical marker for Alzheimer's disease. When one of skill in the art observes differential expression of the claimed peptide between Alzheimer's disease patients and non-diseased patients; one of skill in the art would connect this peptide with potential diagnostic and/or therapeutics for Alzheimer's disease.

Thus, Applicants respectfully submit that since the specification demonstrates a link between the claimed peptide (SEQ ID NO:3) and Alzheimer's disease and that this link connotes the use of the claimed peptide in potential diagnostics and/or therapeutics of Alzheimer's disease, the requirement of "how to use" under 35 USC 122, first paragraph is satisfied.

Furthermore, Applicants respectfully submit that one of ordinary skill in the art would find the suggestion of a link between the claimed peptide (SEQ ID NO:3) and Alzheimer's disease to be reasonable.

The claimed peptide is identified as a fragment of apolipoprotein J precursor protein at page 46, lines 8-18. Apolipoprotein J protein is also known as clusterin; see attached abstract of Moulson et al. (Journal of Cell Physiology 180(3):355-364 1999; reference 2). Clusterin (ApoJ) is a glycoprotein known to be expressed in response to tissue injury and has been associated with the pathology of Alzheimer's disease; see attached abstracts of Giannakopoulos et al. (Acta Neuropathology (Berl) 95(4):387-394 1998; reference 3) and BV Zlokovic (Life Science 59(18):1483-1497 1996; reference 4). It has been suggested that ApoJ exhibits an anti-amyloidogenic effect as it acts as a carrier protein of amyloid beta in body fluids, thus keeping it (amyloid beta) in soluble form (BV Zlokovic Life Science 59(18):1483-1497 1996; reference 4). Soluble amyloid beta is not deposited to form the amyloid plaques which are characteristic of Alzheimer's disease. It has also been suggested that low cellular expression of clusterin may be associated with the neuronal degeneration and death seen in Alzheimer's disease (Giannakopoulos et al. Acta Neuropathology (Berl) 95(4):387-394 1998; reference 3). A skilled artisan would find the data disclosed by the instant inventors to be reasonable since lack of ApoJ (claimed biopolymer marker) is associated with the pathology of Alzheimer's disease and expression of the claimed biopolymer marker was found to be decreased or absent in samples obtained from Alzheimer's disease patients.

Therefore, one of ordinary skill in the art would recognize the linkage between SEQ ID NO:3 and Alzheimer's disease and thus would also find the suggestion of SEQ ID NO:3 as a marker for Alzheimer's disease entirely reasonable.

The Examiner asserts that the disclosure has not addressed issues taught in the prior art as crucial to the discovery of a biopolymer marker.

The Examiner cites an article Hampel *et al* (Journal of Neural Transmission 111:247-272 2004) which is allegedly relevant to the instant invention. According to the Examiner, Hampel *et al* reports on the difficulty involved in the discovery of marker candidates for Alzheimer's. The Examiner states that several required criteria must be met when determining a marker for Alzheimer's, including; indication of disease progression, heterogeneity of the clinical population, feasibility of testing, assay sensitivity, frequency of assessments, stability, standardization, dynamic range and comparative analysis. The Examiner seems to believe that since the specification allegedly lacks any of the criteria stated in the Hampel *et al* reference, it would require undue experimentation for one skilled in the art to make and use the invention.

Applicants respectfully assert that the criteria suggested by Hampel *et al* do not control the issue of enablement with regard to the instant invention. The guidelines for a "test of enablement"

indicate that if a statement of utility in the specification contains within it a connotation of how to use, 35 USC 112 is satisfied. Applicants claim that the presence of a biopolymer marker peptide (SEQ ID NO:3)is linked to Alzheimer's disease; a statement which is enabled by the data presented in Figures 1 and 3. The claimed method involves a simple observation of the presence of the marker (as shown in Figure 3) in a gel, and conducting mass spectrometry analysis to identify the markers present in the gel. Hampel et al. disclose a study similar to that of the instant inventors; see page 260, last paragraph. In this study the content of body fluid obtained from MCI (mild cognitive impairment) patients was compared with the content of body fluid obtained from normal control patients. The MCI patients showed an elevated level of a protein, p-tau_{231}, in comparison to the healthy control patients. Hampel et al. deemed the results of this study adequate to suggest that high levels of p-tau_{231} may be a predictor for progressive cognitive decline in subjects with MCI. This disclosure of Hampel et al. demonstrates further that when elevated levels of proteins are found associated with a disease state, the protein is considered useful for potential diagnostics and/or therapeutics in the disease condition. Thus, in contrast to the Examiner's assertion, the article of Hampel et al. lends support to the argument that the instant invention is enabled. Based upon the above-discussion, Applicants respectfully submit that compliance

with the "required" criteria for a diagnostic assay according to Hampel *et al* is not necessary to show that the instant invention is enabled. When subjected to the "test for enablement" the Examiner's argument is not sufficient to support the enablement rejection; since the association of the claimed biopolymer marker (SEQ ID NO:3)with Alzheimer's disease carries with it a connotation of use for diagnostics.

Similarly, the Examiner cites another article, Tockman *et al* (Cancer Research Supplement 52:2711s-2718s 1992) which is deemed to teach conditions necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. The reference is drawn to biomarkers for early lung cancer detection, however the basic principles are applicable to other oncogenic disorders, according to the Examiner. Tockman *et al* is deemed to teach that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials. Early stage markers of carcinogenesis have clear biological plausiblity as markers of pre-clinical cancer if validated to a known cancer outcome. Tockman *et al* is deemed to teach that the essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from

subjects monitored in advance of clinical disease and link those marker results with histological confirmation of disease.

Applicants respectfully disagree with the Examiner's reliance on the article by Tockman et al.

The Tockman *et al* article is concerned with early detection of lung cancer biomarkers and apparently does not discuss biomarkers for Alzheimer's disease.

Tockman et al. link several biopolymer markers to lung cancer in a manner analogous to that of the instant specification. Tockman et al. state at page 2712s, left column:

"A functional membrane-associated bombesin receptor recently has been isolated from human small cell lung carcinoma (NCI-H345) cells (23), and bombesin-like peptides have been found in the bronchial lavage fluid of asymptomatic cigarette smokers (24). Thus markers of growth factor expression, insofar as they reflect oncogene activation, may also hold promise for the detection of early (preneoplastic) lung cancer."

From this statement, it is clearly evident that Tockman et al. link bombesin with small cell lung cancer and associate it with potential diagnostics for small cell lung cancer. It does not appear that bombesin was "validated" and/or subjected to any "criteria" prior to this association.

Additionally, Tockman et al. state at page 2713s, left column:

"Evidence of a transformed genome, by expression of tumor-

associated antigens, oncofetal growth factors, or specific chromosomal deletions has clear biological plausibility as a marker of preclinical lung cancer."

From this statement, it appears that Tockman et al. believe that the expression of certain proteins provides evidence of a transformed genome and since this transformed genome is associated with lung cancer, it is reasonable to believe that these certain proteins are potential markers.

Such parallel reasoning between Tockman et al. and the instant specification, further supports Applicants contention that one of ordinary skill in the art would not have any difficulty seeing a link between the claimed biopolymer marker peptide (SEQ ID NO:3) and Alzheimer's disease.

It is noted that in chemical and biotechnical applications, evidence actually submitted to the FDA to obtain approval for clinical trials may be submitted to support enablement of an invention. However, considerations made by the FDA for approving clinical trials are different from those made by the PTO in determining whether a claim is enabled (see *Scott v. Finney* 32 USPQ 2d 1115 and MPEP 2164.05).

The Examiner is reminded that the considerations made by the PTO involving clinical trials are less stringent than the considerations made by the FDA. Evidence presented by applicant to provide enablement of an invention need only be convincing to one

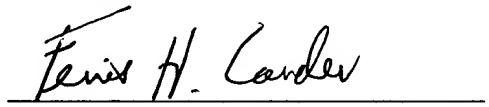
of skill in the art and not conclusive. Thus, Applicants respectfully submit that compliance with the "criteria" of Tockman et al. is not necessary in order to show that the instant invention is enabled.

In conclusion, Applicants claim that the differential expression of SEQ ID NO:3 between Alzheimer's patients and patients age matched with the Alzheimer's patients evidences a link between the claimed peptide (SEQ ID NO:3) and Alzheimer's disease; a statement which is enabled by the instant specification, as evidenced by the arguments presented herein. Applicants assert that one of ordinary skill in the art when reviewing the instant specification, given the level of knowledge and skill in the art, would recognize the link between the claimed biopolymer marker (SEQ ID NO:3) and Alzheimer's disease and would further recognize how to use the claimed peptide (SEQ ID NO:3) as a marker for Alzheimer's disease. Thus, Applicants respectfully request that this rejection under 35 USC 112, first paragraph now be withdrawn.

CONCLUSION

In light of the foregoing remarks, amendments to the specification and amendments to the claims, it is respectfully submitted that the Examiner will now find the claims of the application allowable. Favorable reconsideration of the application is courteously requested.

Respectfully submitted,



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